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VIA FEDERAL EXPRESS

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: **Docket 78N-036L - Citizen Petition 1978N-0036L/CP28**

Response by C.B. Fleet Company, Incorporated, to Comments filed by Braintree Laboratories, Inc. - C207

Dear Sir/Madam:

We represent C.B. Fleet Company, Incorporated, of Lynchburg, Virginia ("C.B. Fleet"). On June 25, 2003, we submitted on behalf of C.B. Fleet the above-referenced Citizen Petition. We have recently become aware of comments on this Citizen Petition filed on December 10, 2003, by Braintree Laboratories, Inc. ("Braintree"). The purpose of this submission is to respond to the allegations and misrepresentations contained in the comments filed by Braintree.

As a preface to these responses, we wish to note that Braintree's comments on this Citizen Petition raise many of the same issues it has raised in response to previous C.B. Fleet petitions and in their own Citizen Petition (CP00P-1472) filed on August 23, 2000, which was denied in large part by the Agency by letter dated July 19, 2001, attached as Exhibit F to the Citizen Petition in this docket. It is part of a continuing

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campaign by Braintree to call into question the safety and efficacy of Fleet® Phospho-soda® (Sodium Phosphates Oral Solution), and its availability as an OTC product for use by professional labeling as a bowel cleanser.

Despite this campaign, Fleet® Phospho-soda® has gained wide acceptance as a bowel cleanser, and both clinical studies and clinical experience have demonstrated it to be safe and effective when used as directed. Fleet has worked with the Agency to address concerns it has raised about the product, such as container size, labeling and other issues. This Citizen Petition was submitted in response to the Agency's request in its letter dated March 1, 1996 (Exhibit D to the Citizen Petition) for additional data on electrolyte and volume changes after administration of two 45 mL doses of the product 10-12 hours apart.

In these comments, C.B. Fleet submits additional safety data, as well as responses to each of the comments in Braintree's submission.

In their comments, Braintree argued that "the administration of double dose sodium phosphates oral solution is not safe, primarily due to dangerous electrolyte shifts." In support of their contention, they provided comments on two clinical studies submitted by C.B. Fleet in support of the subject Citizen Petition (Fleet PS-9902; Fleet F00.020), comments on the Summary and Benefit-Risk Section of the Citizen Petition and on the Discussion Section in which they argued that (1) "patients with any renal impairment (such as the elderly) that are not properly evaluated are clearly at greater risk" [of hyperphosphatemia and calcium phosphate crystalluria]; (2) " the problems of

both unpredictable effects in the elderly and maladministration are likely to continue to be refractory to changes made to the Fleet® Phospho-soda® labeling (since this requires that practitioners be aware of labeling in the first place)" and (3) " since the marketing of the Fleet® Phospho-soda® double dose regimen has continued unabated with new kits being devised, additional adverse events of increasing severity can be expected." Each of these items will be addressed below.

1. Updated Data on Clinical Experience Continue to Demonstrate that Fleet® Phospho-soda® is Safe

As part of the June 25, 2003, Citizen Petition, Fleet submitted data which showed that in the United States the Serious Adverse Experience (SAE) Rate for Fleet® Phospho-soda® for the years 1991-2002 was 1.46 per million bowel cleansing doses sold (See Table 6, page 40 of the Citizen Petition). C. B. Fleet has updated this Table to include the year 2003; the results are provided in Exhibit A.

The overall SAE rate for the 13-year period from 1991 through 2003 is 1.58 per million bowel-cleansing doses sold. Braintree states in their comments that the C.B. Fleet Petition "dismisses" adverse experiences as "very rare." In fact, an incidence of a SAE less than 1 per 10,000 is classified as "very rare" by the CIOMS Working Group on Benefit-Risk Balance for Marketed Drugs (Exhibit B). As can be seen from the data assembled by C.B. Fleet, the SAE rate for Fleet® Phospho-soda® is over one order of magnitude lower than that which is categorized as "very rare" by this distinguished international body of experts.

In addition, C.B. Fleet does not "dismiss" SAE's, as Braintree suggested. Rather, C.B. Fleet is constantly working to make the bowel cleansing process using Fleet® Phospho-soda® as safe as possible. To illustrate, in their comments Braintree states that the ACCU-PREP® kit will lead to additional adverse events of increasing severity. In fact, to this date, there have been **no** SAE's reported for this kit, which has been marketed since January 2003. The professional advertising material submitted to the Agency by Braintree in their comments shows that Professional Use Warnings and Precautions were made available to healthcare professionals, as were a free videotape with patient instructions and information on the availability of a website, www.phosphosoda.com, which provides additional information to healthcare professionals and consumers. The ACCU-PREP® kit was specifically designed to make the bowel-cleansing process **safer** by designing hydration into the process by standardizing the instructions to physicians, and by making the process easier for the patient to understand. Thus, this new product was introduced to make the bowel cleansing process safer; clinical experience, based on spontaneous adverse event reporting, has demonstrated that to be the case.

2. The Electrolyte Levels Reported in Fleet Study PS-9902 Do Not Raise Any Significant Safety Issues.

Braintree raises several arguments about C.B. Fleet Study PS-9902, specifically calling into question the ranges of acceptable electrolyte levels set forth in the protocol and used in the Study and alleging that the results on potassium levels raise a significant risk, particularly in female patients.

C.B. Fleet believes the ranges of electrolyte levels specified in this study were appropriate.

In the study, hyperphosphatemia as an adverse experience was defined as serum phosphorus greater than 8.6 mg/dL. Hypocalcemia was defined as serum calcium less than or equal to 8.0 mg/dL, while hypokalemia was defined as serum potassium less than or equal to 3.5 mEq/L. In their comments, Braintree provided a copy of the Massachusetts General Hospital Normal Reference Laboratory Values which show the upper limit of normal for phosphorus to be 4.5 mg/dL, the lower limit of normal for calcium to be 8.5 mg/dL and the lower limit of normal for potassium to be 3.5 mEq/L. In the underlying design for this study, there was an assumption that an out of normal result for an electrolyte was not necessarily in and of itself an adverse event. The National Cancer Institute Common Toxicity Criteria Manual (1999 edition) (Exhibit C) was used to help define what electrolyte changes constituted an adverse event. For potassium, the most critical electrolyte, the protocol definition for the study and the NCI definition of an adverse event were identical. For calcium, the NCI value for a Grade 1 (mild) adverse event was chosen as the threshold. For phosphorus, the NCI criteria did not have a definition for hyperphosphatemia as an adverse event. There is a general recognition that the signs and symptoms of acute hyperphosphatemia are due to the effects of hypocalcemia, and would be reflected as such. Hence, a value of approximately two times the upper limit of normal was chosen as the threshold for classification as an

adverse event for hyperphosphatemia. The ranges for acceptable levels of electrolytes were thus entirely appropriate.

Whether or not there is agreement with these classifications, the important fact is that **none** of the patients in this study suffered an SAE. In fact, as was described in the Citizen Petition, none of the over two thousand subjects who have been enrolled in published clinical studies of Fleet® Phospho-soda® have suffered an SAE. The electrolyte changes that occur following a 2 x 45 mL (and the 2 x 30 mL) bowel preparation regimen administered 10-12 hours apart with Fleet® Phospho-soda® are transient, and electrolyte levels quickly return to normal.

As to the results relating to hypokalemia, Braintree states that "of greater concern, the report further observes that persistent hypokalemia occurred in 10% of Fleet® Phospho-soda® prepared patients (see page 69 of PS-9902 report)" and "further analysis is required, particularly for female patients." C.B. Fleet believes the data in the referenced study shows that the hypokalemia which was observed at the follow-up visit was transitory and asymptomatic. At this time point, 24 hours after colonoscopy, 16 of 149 patients (11%) showed a serum potassium level below the lower limit of normal, defined as 3.6 mEq/L, the value used by the clinical laboratory which conducted the majority of analyses in this study. [Note: this includes 5 patients with serum potassium of 3.5 mEq/L, a value which would be considered normal by the Massachusetts General Hospital reference values provided by Braintree in their comments to the Citizen Petition.] For 15 of these patients, the degree of hypokalemia was classified as mild

(range of 3.1 to 3.5 mEq/L) as defined by the NCI toxicity criteria. For one patient, a 62 year old male, the potassium level at follow-up was 2.9 mEq/L, which is marginally in the range considered to be a severe adverse event by NCI criteria. This patient, as well as all of the other patients in the study, did not suffer any serious adverse experience. For the majority of all patients in the study who took Fleet® Phospho-soda®, there was an increase in serum potassium in the 24 hours between the post-preparation visit and the follow-up visit (mean change from 3.8 to 4.0 mEq/L), which is much more supportive of a rapid return to normal values than the maintenance of a persistent condition.

As stated in the main body of the Citizen Petition (page 24), on an overall basis, the results of two submitted studies (PS-9902; F00.020) showed that gender, dose and age were not significant predictors of the change in serum potassium, although females exhibited a significantly larger variation in change than did males. There is no indication in either of these studies of any clinically significant adverse event in either males or females attributable to hypokalemia. The three lowest recorded serum potassium values recorded in the PS-9902 study were 2.8, 2.9 and 2.9 mEq/L and these occurred in a 33 year old female, a 52 year old male and a 62 year old male, respectively.

3. The Results from Study F00.02 Do Not Raise Any Issues With Regard To Electrolyte Levels, Transfer of Calcium From Hard Tissue or Increases in QTc Intervals

Braintree raises three issues with regard to the pharmacokinetic study - F00.02 - submitted by C.B. Fleet. First of all, they argue that the results include abnormal electrolyte levels. Second, they assert that the increased serum calcium levels at the 72

hour measurement may represent mobilization of calcium from hard tissue, as indicated by a progressive increase in alkaline phosphate levels. Last, they assert the electro-cardiogram ("EKG") results show abnormalities associated with changes in calcium and potassium levels.

As to the electrolyte results, Braintree notes that "of significant concern, following the final sodium phosphates dose, a number of study subjects show progressively higher serum calcium levels: as much as 0.5 mg/dL above baseline at the final 72 hour measurement (see figure 4, page 35, F00.020 study)." Figure 2 of this same reference shows that the mean calcium level at the final measurement was well within normal limits. There were, however, no reports of hypercalcemia; as can be seen in Exhibit D, the calcium levels for all subjects were within normal limits at 24 hours after the administration of the first dose of Fleet® Phospho-soda® and remained within normal limits through the end of the 84 hour experimental period. These findings raise no significant safety issue.

Second, as to potential mobilization of calcium from hard tissue, this is a normal event in response to persistent decreased serum calcium levels. There is no evidence to suggest that this effect, if it does occur, is anything other than transient or is clinically meaningful in the context of bowel-cleansing, a process which most patients undergo on an infrequent basis. As was stated above, hypercalcemia did not occur.

Last, as to the QTc results, Braintree states that 18 study subjects showed abnormalities in their post-preparation EKG with an increase in QTc interval. Actually,

the data (Table 5 page 41 of Exhibit B, Citizen Petition) shows 7 subjects (29.2%) with a transient borderline increase and 2 subjects (8.3%) with a transient prolonged increase. All values had returned to normal by the end of the study. In any event, at no time did the QTc value for any subject at any time point exceed the NCI threshold value of 0.48 seconds, nor were any arrhythmias noted. In addition, appended to this document is an evaluation by an expert cardiologist who examined the data and concluded: "It is my opinion that there is a negligible risk for arrhythmias when sodium phosphate is used as a bowel cleansing agent." (Exhibit E) This again is a non-issue.

4. Braintree's Comments on the Summary and Benefit-Risk Evaluations Submitted by C.B. Fleet in the Citizen Petition as to Maladministration and Use in the Elderly Are Both Outdated and Unfounded.

In this section of their comments, Braintree states: "Fleet states that most of the adverse effects reported in the literature represent incorrect administration or use in patients with contraindications, implying that this experience is somehow not relevant since the product is labeled against these uses." C.B. Fleet does not believe that there is any implication that the "adverse effects" are not relevant. In this instance, Braintree seems to be confusing "adverse effects" with "serious adverse experiences." Again, as is shown in Exhibit A, in the United States there have been a total of 61 SAEs over 13 years at a rate of 1.58 per million bowel cleansing doses sold. They should be viewed in the context of approximately 40 million bowel-cleansing doses sold during that period. Analysis of these cases demonstrates that, for the most part, these events occurred as a result of overdosing or use in patients where use of the product is contraindicated. This is

simply a statement of fact (See Exhibit H in Citizen Petition); it is not meant to sweep aside the issue of what occurs when the product is not properly used.

The major contention made by Braintree is that there is a significant problem of physician maladministration of Fleet® Phospho-soda®. To support this statement, they cite a study by Chan and co-workers of Canadian gastroenterologists in which the authors reported that 55% of those using the Fleet® Phospho-soda® preparation reported that they did not exclude its use in patients with renal failure and 70 % reported that they did not exclude its use in patients with cardiovascular disease. From this, Braintree concludes that "actual practice rarely includes an adequate evaluation for contraindications." Also on this theme, Braintree states that "due to the OTC status of oral phosphates solutions, a presumption of safety exists among consumers and practitioners which makes maladministration a likely event." This final statement is belied by the usage and SAE incidence data that is attached to this response and which demonstrates the high degree of safety inherent in the 2 x 45-mL dosage bowel-cleansing procedure. Even if Braintree's contention is true, which C.B. Fleet does not believe to be the case, then the very rare SAE incidence would be existing in a milieu of significant "maladministration" by physicians.

The Chan paper was received for publication on June 4, 1996. While not stated in the paper itself, it would be reasonable to assume that the survey itself was conducted no later than the early part of 1996, if not much earlier, and, hence, over eight years ago. Referring to data in Exhibit A, it can be seen that from 1991 to 1995, approximately 6.5 million

bowel-cleansing doses of Fleet® Phospho-soda® had been sold; subsequent to that date, through the end of 2003, an additional 32 million doses were sold. This illustrates that at the time of the Chan publication, usage and experience with the 2 x 45 mL regimen were not as extensive as at the present time. (This dosing regimen did not become widespread until 1991, after the publication by Vanner of its use).

There have been a large number of papers published addressing issues relating to the safe and effective use of the product subsequent to 1995 (See Exhibit H in Citizen Petition). Further, instructions for safe use of the 2 x 45 mL regimen have been published by C.B. Fleet (such as on C.B. Fleet's website) and by independent, authoritative bodies.

Significantly, the American Society for Gastrointestinal Endoscopy (ASGE) has published a status evaluation paper on colonoscopy preparations (Exhibit F) in which technology committee members discussed and evaluated bowel cleansing products. In its summary, this independent group concluded,

> "The choice of a bowel preparation for colonoscopy is influenced by cleansing effectiveness, safety, ease of completion, side effects, patient tolerance, and cost. Although PEG-ELS and NaP are equally effective in colonic cleansing, NaP is better tolerated. However, NaP may be contraindicated in certain patient populations. The selection of a colonoscopy preparation requires clinical judgment and informed patient preference."

The group also reported that the alternative to sodium phosphate, polyethylene glycol – electrolyte lavage solution, a product marketed by Braintree, was not without its safety issues:

> "However, rare adverse events have been reported after PEG-ELS including nausea, abdominal pain, aspiration of the solution, Mallory-Weiss tear, toxic colitis, PEG-induced pancreatitis, lavage induced pill malabsorption, syndrome of inappropriate secretion of antidiuretic hormone and cardiac arrythmias."

Similar to the ASGE position, in a recent editorial on "The appropriate use of sodium phosphates oral solutions," Love concluded that "the bowel-cleansing regimen described by Vanner is safe and effective and offers an alternative to patients." (The Vanner regimen is the 2 x 45 mL dosing, with the doses separated by 10-12 hours.) (See Exhibit G).

Fleet disagrees with Braintree's contention that the problems of maladministration are likely to continue to be refractory to changes made to labeling for Fleet® Phospho-soda®, since this requires that practitioners be aware of the labeling in the first place. This argument is based on the results of a now outdated paper (Chan), and ignores the fact that numerous articles and position statements by authoritative bodies have been published subsequent to the Chan survey, as well as C.B. Fleet's efforts to educate physicians on proper use, and significant physician experience with the regimen. C.B. Fleet has taken steps to promote the appropriate use of Fleet® Phospho-soda®, including a website, videos, publication of warnings and contraindications in the *Physicians' Desk*

Reference, and participation by C.B. Fleet Medical Affairs personnel in professional meetings and associations. In 2004, C. B. Fleet will attend over 30 such meetings.

Braintree's allegation that there is a significant problem with maladministration is based on outdated data and is not reflected in clinical experience with the product. Adverse events and improper use occur with the use of any drug, including with Braintree's bowel cleansing products; all a responsible company can do is educate the profession through labeling, advertising and other promotional and educational efforts as to proper use of the product. Both C.B. Fleet published information and information from third party professional bodies have addressed the proper use of the product for bowel cleansing. In addition, extensive clinical experience has made physicians aware of proper use of the product. If maladministration were the significant issue that Braintree believes it is, it would be evident from clinical experience. As noted, the opposite is true.

The other issue raised by Braintree is use of Fleet® Phospho-soda® in the elderly. In their discussion of this issue, Braintree emphasizes their contention that elderly individuals in particular are susceptible to adverse effects from sodium phosphates bowel preparation. In support of this, they provide a reference by Beloosesky *et. al.* describing a study of 36 hospitalized geriatric patients, with a mean age of 80.5 years. The authors concluded that sodium phosphate induces serious electrolyte abnormalities in the elderly, and advised assessment of serum electrolytes, phosphorus and calcium prior to sodium phosphate preparation. C.B. Fleet agrees that in elderly patients such as those described by Beloosesky, where 44% of the individuals were moderately or severely demented and

a significant percentage had major coexistent diseases, assessment of their conditions including laboratory workups should be performed prior to bowel-cleansing with Fleet® Phospho-soda®. In spite of the occurrence of hypokalemia and hypocalcemia, the authors reported that none of these patients suffered severe complications.

In addition, Braintree totally disregards what is stated in the proposed professional labeling as to this issue. C.B. Fleet has proposed, as noted on pages 2 and 3 of the Citizen Petition, that:

> (B) "**Use with Caution**" [these three words in bold print] "in patients with impaired renal function, heart disease, acute myocardial infarction, unstable angina, pre-existing electrolyte disturbances, increased risk for electrolyte disturbances (e.g., dehydration, gastric retention, bowel perforation, colitis, ileus, inability to take adequate oral fluid, concomitant use of diuretics or other medications that affect electrolytes), with debilitated or **elderly patients** or with patients who are taking medications known to prolong the QT interval."
>
> (C) "**In at-risk patients, including elderly patients, consider obtaining baseline and post-treatment sodium, potassium, calcium, chloride, bicarbonate, phosphate, blood urea nitrogen, and creatinine values, and consider using the lower end of the dosage range.** [this sentence in bold print]. There is a risk of elevated serum levels of sodium and phosphate and decreased levels of calcium and potassium; consequently hypocalcemia, hypokalemia, hyperphosphatemia, hypernatremia, and acidosis may occur."

(Emphasis Added).

Furthermore, in a 72 hospitalized patient comparative study (37 sodium phosphates; 35 PEG-ELS) conducted in elderly patients (mean age of 84; range of 80-93), Seinela *et. al.* (Exhibit H) found that sodium phosphates and PEG are almost equally

tolerated and effective in very old patients. Sodium phosphates preparations caused more changes in the levels of potassium and sodium. Patients' subjective opinions favored sodium phosphates. These authors recommended PEG-ELS preparation for those elderly patients who are vulnerable to complications caused by electrolyte disturbances. No clinically significant complications occurred during the preparations or the endoscopies.

The American Society for Gastrointestinal Endoscopy has published a guideline, "Modifications in endoscopic practice for the elderly" (Exhibit I), which addresses the issue of pre-procedure preparation. This group of experts states that preparation for endoscopy in the geriatric or aged populations differs little from that in younger adults. Either large volume PEG-ELS lavage or sodium phosphates osmotic laxative preparations can be used before colonoscopy. They emphasize that caution should be exercised in those patients with renal or cardiac disjunction, in whom fluid and electrolyte shifts can occur with the osmotic preparations.

The issue of the safety of use in the elderly, while significant, has both been overstated by Braintree, but, more importantly, been addressed by C.B. Fleet in the labeling proposed in the Citizen Petition.

5. Braintree's Summary Comparison of the Safety of Fleet® Phospho-soda® to that of Propulsid® is Both Gratuitous and Unfounded, as are its Other References to the Alleged Lack of Safety of Fleet® Phospho-soda®

In the concluding paragraphs of its comments, Braintree compares the safety of Fleet® Phospho-soda® to that of Propulsid®, a drug withdrawn from the market for safety reasons. Such a comparison is entirely gratuitous. Fleet® Phospho-soda® has

been marketed since 1869 as a laxative, since at least 1972 as a bowel cleanser, and since at least 1990 used widely in a regimen of two 45 mL doses administered 10-12 hours apart. In that time, there have been no significant side effects such as those associated with Propulsid®. And, as noted above, there have been no SAEs to the "new kits being devised", i.e., ACCU-PREP®, since its introduction in 2003. To the contrary, as discussed above, the kit was devised to further assure the safe use of the product and further reduce any possible adverse events.

Braintree notes, in conclusion, that "due to unresolved safety problems (particularly nephrocalcinosis and unpredictable hypokalemia which has been demonstrated to be unresponsive to labeling)" that the Citizen Petition should be denied. As to the hypokalemia issue, it is discussed in Section 2 above.

As to nephrocalcinosis, C.B. Fleet is aware of the publication suggesting a relationship of Sodium Phosphates Oral Solution with nephrocalcinosis (Exhibit J). Indeed, C.B. Fleet made the Agency aware of this issue and is addressing it. C.B. Fleet's preliminary analysis is that not only is that condition extremely rare, but it may result from the use of ACE inhibitors, ARB's and/or diuretics and/or inadequate hydration. C.B. Fleet has indicated to the Agency that it will address this issue by appropriate studies and professional education. Such information will be submitted when it becomes available.

6. Conclusion

In summary, C.B. Fleet does not believe that the issues raised by Braintree in its comments call into question the safety of either the 2 x 30 mL or 2 x 45 mL dosing of Fleet® Phospho-soda® administered 10-12 hours apart. Braintree has neither submitted any data nor made any credible argument that should prevent the Agency from granting this Citizen Petition, with the labeling proposed by C.B. Fleet. C.B. Fleet has fully responded to the Agency's March 1, 1996, request to demonstrate the safety of the 2 x 45 mL dosing administered 10-12 hours apart, and the changes in the Monograph on Laxative Drug Products for OTC Human Use requested therein should be accepted.

Respectfully submitted,

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